PCT/GB 2004 / 0 0 5 2 6 3

10 JANUARY 2005

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Signed P. Mahoney

Dated 17 December 2004

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Request for grant of a patent

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1. Your reference — AFB/JAS/P9621GB

240EC03 E861828-3 000571
P01/7700 0.00-0329854.4 CHEQUE
23 DEC 2003

2. Patent application number *(The Patent Office will fill this p)* — 0329854.4

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

TEMREL INC.
9 Myrtle Street
Douglas
Isle of Man IM1 1ED

Patents ADP number *(if you know it)* 8778557001

If the applicant is a corporate body, give the country/state of its incorporation — British Virgin Islands

4. Title of the invention — PROCESS FOR PRODUCING PARTICLES FOR PHARMACEUTICAL COMPOSITIONS

5. Name of your agent *(if you have one)* — W. H. Beck, Greener & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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16bal
6/12/03

Patents ADP number *(if you know it)* ~~323001~~ / 08991754001

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(If you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

Yes

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	
Description	10
Claim(s)	5
Abstract	1
Drawing(s)	3

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature(s) Date 23.12.03

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

Dr. James Stones - (020) 7693 5600

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Process for Prcducing Particles for Pharmaceutical Compositions

The present invention relates to a process to produce particles, particularly for use in pharmaceutical compositions. In particular, the invention relates to the use of water to control particle size in a composition comprising prednisolone metabisulphobenzoate or a pharmacologically acceptable salt thereof.

US-A-5834021 (Speirs; published on 10th November 1998) discloses a non-disintegratable solid enteric composition comprising 5 wt % prednisolone metasulphobenzoate ("Pred-MSB") in an excipient matrix comprising 40 wt % microcrystalline cellulose, 35 wt % lactose and 20 wt % croscarmellose sodium. The composition is in the form of pellets having a diameter in the range of 1000 to 1400 μm. The pellets are formed by dry mixing the Pred-MSB with the cellulose, the lactose and the croscarmellose sodium. Water is added to the mixture which is then stirred for 10 minutes to form an extrudable paste. The paste is extruded from a 25 mm diameter bowl through a 1 mm diameter tube of about 5 mm length at a rate of about 100 mm/min and spheronised on an 8 in (20 cm) plate rotated at about 1000 rpm for 10 to 15 minutes to provide said pellets. The resultant pellets are dried at 50°C for 30 min on a fluidised bed. The pellets are then coated with an Eudragit™ S100 (available from Röhm Pharma GmbH, Darmstadt, Germany) coating to provide a theoretical weight gain on coating of 11.6% and filled (15.7 mg per capsule) into size 1 hard gelatin capsules. The filled capsules are coated with an Eudragit™ L100 (also available from Röhm Pharma GmbH) coating to provide a theoretical weight gain on coating of 10.2%. The coated capsules may be used as a delayed and sustained release oral treatment of inflammatory bowel disease ("IBD").

Similar treatments of IBD are described in UK patent application Nos. 0215656.0 and 0215657.8 (Speirs; unpublished). The contents of

US-A-5834021, GB0215656.0 and GB0215657.8 are incorporated herein by reference.

The diameter of the pellets is usually in the range between from about 500 to 2500 μm, preferably 800 to 1700 μm, more preferably 800 to 1500 μm and still more preferably 1000 to 1500 μm. However, it should be appreciated that pellets may have a diameter anywhere within the aforementioned ranges and that a capsule may have pellets having a range of diameters. One reason pellets of this size are preferred is that they may be coated satisfactorily with, for example, an enteric coating. Such enterically-coated pellets display the required release profile in the intestines. Smaller pellets tend to be less spherical and more elongated and may be below the required size to allow homogeneous filling of capsules while retaining a sufficient number to distribute through the bowel. The preferred size ranges have been justified by bioscintigraphy, the results of which showing that 200 or so pellets obtained an appropriate spread throughout the bowel.

The process disclosed in US-A-5834021 produces a range of pellet sizes. The pellets have to be screened so that the pellets of required size can be collected. Pellets that are either too large or too small to be used effectively in the delayed and sustained release capsules would normally be discarded resulting in significant wastage. Such wastage is obviously undesirable. There is a need therefore for an improved process that produces particles having a more favourable distribution of particle sizes that is more particles within the required diameter range, resulting in a reduction in the amount of wastage.

The inventors have discovered that even small variations, e.g. ±5 wt %, in the amount of water used in the above-mentioned process causes a significant change in the size of the particles and the distribution of particle sizes. With this in mind, the inventors reasoned that particle size

and, more importantly, particle size distribution is dependant on the amount of water used. The inventors realised that the amount of water could, therefore, be used to control the particle size and distribution. In this way, particles having different ranges of sizes could be produced.

According to a first aspect of the present invention, there is provided use of water to control particle size in a process comprising:

mixing water with a component composition comprising at least prednisolone or a pharmacologically acceptable salt or derivative thereof and a rheology modifying agent to produce a paste;

extruding at least a portion of the paste to form extrudate;

spheronising at least a portion of the extrudate to form spheronised particles; and

drying at least a portion of the spheronised particles.

The term "paste" is intended to include wet granulate.

The particles of the present invention are typically pellets or granules. In preferred embodiments, the composition further comprises sugar and cellulose.

Without wishing to be bound by any particular theory, the amount of water affects particle size due to the state of hydration of the matrix of the particle. Once the amount of water passes a certain point, the matrix is too wet and forms large agglomerates. It would appear that a large amount of water is taken up by the rheology modifying agent. Beyond the saturation point for this process, the amount of water appears critical.

One advantage of the present invention is that more particles having a diameter within the required range, usually 800 to 1500 μm, are produced. Different pluralities of preferred pellets of this size may be treated/coated using different modalities or thicknesses of delayed release

coating material in order to achieve release at specified areas of the bowel. An example of such coated pluralities of pellets is disclosed in PCT/GB03/02911, the disclosure of which is incorporated herein by reference.

Such coated pluralities of pellets allow a number of clinical objectives to be met. For example, they allow continuous delivery of a drug to treat large areas of bowel where the drug would otherwise be absorbed or metabolised if suddenly released. In addition, they allow continuous delivery of a drug over a section of the bowel to increase contact with the absorptive mucosa thereby allowing maximum absorption whereas the drug would be broken down if otherwise released in one section. Further, where a drug at high concentration would be toxic to the gut mucosa, the pellets allow the drug to be continually available at low concentration thereby allowing absorption without or with reduced toxicity.

Water is usually used in an amount of between from about 180 wt % to about 190 wt % of the component composition and is preferably used in an amount of about 185 wt % of the component composition. The inventors found the amount of water used in the process to form the matrix by absorption to be surprisingly large. This large amount of water distinguishes the present invention over all other pelletting processes of which the inventors are aware.

Usually from about 80 % to about 98 % of particles and typically between from about 90 to 98 % of particles, have a diameter between the range of about 800 to about 1500 microns. Even though the number of particles whose diameter is within the required range is greater than for the process disclosed in US-A-5834021, the dry particles may be screened to obtain particles having a diameter with the range of about 800 to about 1500 μm and to remove particles whose diameter does not fall within that

range.

Use of about 5 wt % less water usually reduces particle size significantly. Conversely, use of 5 wt % more water increases particle size such that 100% of particles have a diameter greater than 1500 μm which is useless if the pellets are to be enterically coated and used to release the active into the bowels.

The use of less water reduces the particle size distribution such that fewer particles have a diameter within the desired 800 to 1500 μm range and the mean particle size is reduced. The use of more water increases particle size distribution until all pellets are greater than 1500 μm. Thus, the present invention increases the number of useful particles and reduces the amount of waste.

The therapeutically active compound is prednisolone or pharmacologically acceptable salt or derivative thereof. A suitable salt is prednisolone sodium metasulphobenzoate. In this case, the particles may be used to treat inflammatory bowel disease, for example, in a delayed and sustained release oral medicament.

Prednisolone or the therapeutically acceptable salt or derivative thereof may be present in an amount between from more than 0 wt % to about 90 wt%, preferably between from more than 0 wt % to about 40 wt %, and more preferably between from about 5 wt % to about 20 wt % of the component composition. In one embodiment, the prednisolone is present in an amount of about 5 wt %.

The component composition preferably consists essentially of prednisolone or a pharmacologically acceptable salt or derivative thereof, rheology modifying agent, sugar and cellulose.

The rheology modifying agent swells upon hydration to form a gel-like matrix having visco-elastic properties. A preferred rheology modifying agent is croscarmellose sodium, e.g. Ac-Di-Sol™ (FMC Biopolymer, 1735 Market Street, Philadelphia, PA 19103, USA). Croscarmellose sodium is usually used as a super disintegrant, i.e. a compound that assists dissolution of a composition. It is, therefore, surprising and totally unexpected that a super disintegrant would form a gel-like matrix. The rheology modifying agent is present in an amount of at least 5 wt % of the component composition, preferably at least 10 wt % and more preferably in an amount of between from about 10 to about 40 wt %, e.g. 20 wt %, of the component composition.

The sugar is preferably lactose monohydrate. The sugar is preferably present in an amount of between from about 30 to about 50 wt %, e.g. 35 wt %, of the component composition.

The cellulose is preferably microcrystalline cellulose. The cellulose is preferably present in an amount of between from about 35 to about 45 wt %, e.g. 30 wt %, of the component composition.

The speed of the spheroniser is very slow in comparison to that in known pellet manufacturing processes. For the purposes of the present invention, the spheronising plate usually rotates at between from about 125 rpm to about 2000 rpm, preferably about 200 rpm to about 1000 rpm and, if the speed of rotation used is outside this range then the spheroniser usually fails to make pellets. In addition, with knowledge of known processes, the use of a smaller spheronising plate would intuitively require a faster rotation speed. However, in the present invention, the reverse is true and a smaller plate requires a faster speed of rotation. To the inventors' knowledge, this observation is unique in pellet manufacturing.

Controlling the amount of water used allows optimisation of the size distribution of particles at maximum process yields. The particles are intended for a particular purpose, for example medical treatment of a condition, e.g. IBD.

The resultant particles may be coated with an enteric coating such as Eudragit™ S which is an anionic copolymer of methacrylic acid and methacrylic acid methyl ester in which the ratio of free carboxylic groups to ester groups is approximately 1 : 2 and has a mean molecular weight of 135,000. A plurality of the coated particles may be encapsulated in a capsule or compressed into a tablet. The capsule or tablet may be coated with another enteric coating such as Eudragit™ L which differs from Eudragit S in that the ratio of free carboxylic groups to ester groups is approximately 1 : 1. Both Eudragit™ L and Eudragit™ S are insoluble in gastric juice (about pH 6) but only Eudragit™ L is readily soluble in intestinal juice below about pH 7. In this way, release of the active component is delayed until the colon and sustained to increase the effectiveness of the active. Sustained release is believed to be achieved at least in part through the coating becoming permeable.

It is believed currently that the gel-like matrix is formed from the cellulosic components of the pellets upon rehydration. In preferred embodiments, the cellulosic components are microcrystalline cellulose and croscarmellose sodium (a cellulose derivative). On rehydration, the pellets swell and release the prednisolone in a sustained manner over time. The pellets also become "sticky" on rehydration and stick to the gut wall. As a result, the swollen pellets stick to the target site in the gut thereby increasing the effectiveness of the prednisolone. In addition, the pH within the gut increases from the centre of the gut lumen to the wall of the gut. Where the pellets are coated with a pH dependent release coating material, the rate of release of the prednisolone increases as the pellets approach the gut wall. This feature of preferred embodiments of the

invention may also increase the effectiveness of the prednisolone.

The results also indicate that the overall yield (after drying) of the particles increases as the amount of water used approaches the optimum amount.

In a second aspect of the present invention, there is provided a process for the production of particles for use in a pharmaceutical composition, said process comprising the steps of:

mixing water with a component composition comprising at least prednisolone or a pharmacologically acceptable salt or derivative thereof and a rheology modifying agent to produce a paste;

extruding at least a portion of the paste to form extrudate;

spheronising at least a portion of the extrudate to form spheronised particles; and

drying at least a portion of the spheronised particles.

Preferably, the amount of water used is between from about 180 to about 190 wt % of the weight of the component composition and where the spheronising step uses a rotation 70 cm plate, the plate does not rotate at about 33 rpm.

The process of the second aspect may have any or all of the preferred features of the process defined above, in any appropriate combination.

Preferred embodiments of the present invention will now be described, by way of example only and with reference to the accompanying figures. In the figures:

Figure 1 is a photograph of uncoated pellets produced in Example 1;

Figure 2 is a photograph of uncoated pellets produced in Example

2; and

Figure 3 is a photograph of uncoated pellets produced in Example 3.

Example 1

Prednisolone metasulphobenzoate pellets were prepared by preparing a dry mix of 5 wt% prednisolone sodium metasulphobenzoate, 40 wt% microcrystalline cellulose (Avicel™ PH 101), 35 wt% lactose monohydrate (D80 200 Mesh) and 20 wt% croscarmellose sodium (Ac-Di-Sol™). Purified water (185 wt% of the dry mix components) was added and the resulting mixture mixed for 10 minutes to form and extrudable paste which was then extruded and spheronised. The pellets were then dried in a fluid bed granulator and screened to ensure the size of the particles was in the range 800 to 1500 μm.

Figure 1 depicts the pellets formed by Example 1. The majority of these pellets are within the required range of 800 to 1500 μm.

Example 2

Pellets were formed using the steps described in Example 1 although only 180 wt % water was used instead of 185 wt %. The yield (after drying) of the pellets was 91 %.

Figure 2 depicts the pellets formed by Example 2. The photograph clearly shows that the size of the pellets is reduced significantly when less water is used.

Example 3

Pellets were formed using the steps described in Example 1

although 190 wt % water was used instead of 185 wt %.

Figure 3 depicts the pellets formed by Example 3. The photograph clearly shows that the size of the pellets is increased significantly when more water is used.

Example 4

Pellets were formed using the steps described in Example 1 although only 182.5 wt % water was used instead of 185 wt %. The yield (after drying) of the pellets was 96.5 %.

Example 5

Pellets were formed using the steps described in Example 1 although only 177.5 wt % water was used instead of 185 wt %. The yield (after drying) of the pellets was 85 %.

It will be appreciated that the invention is not restricted to the details described above with reference to the preferred embodiments but that numerous modifications and variations can be made without departing from the spirit or scope of the invention as defined by the following claims.

CLAIMS

1. Use of water to control particle size in a process comprising:

mixing water with a component composition comprising at least prednisolone or a pharmacologically acceptable salt or derivative thereof and a rheology modifying agent to produce a paste;

extruding at least a portion of the paste to form extrudate;

spheronising at least a portion of the extrudate to form spheronised particles; and

drying at least a portion of the spheronised particles.

2. Use as claimed in Claim 1 wherein water is used in an amount of between from about 180 wt % to about 190 wt % of the component composition.

3. Use as claimed in Claim 1 or Claim 2 wherein water is used in an amount of about 185 wt % of the component composition.

4. Use as claimed in any of Claims 1 to 3 wherein between from about 80 % to about 98 % of particles have a diameter between the range of about 800 to about 1500 μm.

5. Use as claimed in any of the preceding claims wherein from about 95 % to about 98 % of particles have a diameter between the range of about 800 to about 1500 μm.

6. Use as claimed in Claim 3 wherein use of 5 wt % more water increases particle size such that substantially all of the particles have a diameter over 1500 μm.

7. Use as claimed in any of the preceding claims wherein the dry particles are screened to obtain particles having a diameter with the range

of about 800 to about 1500 μm.

8. Use as claimed in any of the preceding claims wherein the prednisolone is present in the form of the pharmacologically acceptable salt, prednisolone sodium metasulphobenzoate.

9. Use as claimed in any of the preceding claims wherein the prednisolone or pharmacologically acceptable salt or derivative thereof is present in an amount between from more than 0 wt % to about 90 wt% of the component composition.

10. Use as claimed in any of the preceding claims wherein the prednisolone or pharmacologically acceptable salt or derivative thereof is present in an amount between from more than 0 wt % to about 40 wt% of the component composition.

11. Use as claimed in any of the preceding claims wherein the prednisolone or pharmacologically acceptable salt or derivative thereof is present in an amount between from about 5 wt % to about 20 wt% of the component composition.

12. Use as claimed in any of the preceding claims wherein the prednisolone or pharmacologically acceptable salt or derivative thereof is present in an amount of about 5 wt% of the composition.

13. Use as claimed in any of the preceding claims wherein the rheology modifying agent comprises croscarmellose sodium.

14. Use as claimed in any of the preceding claims wherein the rheology modifying agent is Ac-Di-Sol™.

15. Use as claimed in any of the preceding claims wherein the rheology

modifying agent is present in an amount of at least 5 wt % of the component composition.

16. Use as claimed in any of the preceding claims wherein the rheology modifying agent is present in an amount of at least 10 wt % of the component composition.

17. Use as claimed in any of the preceding claims wherein the rheology modifying agent is present in an amount of between from about 10 to about 40 wt % of the component composition.

18. Use as claimed in any of the preceding claims wherein the rheology modifying agent is present in an amount of about 20 wt % of the component composition.

19. Use as claimed in any of the preceding claims wherein the component composition further comprises sugar.

20. Use as claimed in Claim 19 wherein the sugar is lactose monohydrate.

21. Use as claimed in Claim 19 or Claim 20 wherein the sugar is present in an amount of between from about 30 to about 50 wt % of the composition.

22. Use as claimed in any of Claims 19 to 21 wherein the sugar is present in an amount of about 35 wt % of the component composition.

23. Use as claimed in any of the preceding claims wherein the component composition further comprises cellulose.

24. Use as claimed in Claim 23 wherein the cellulose is microcrystalline

cellulose.

25. Use as claimed in Claim 23 or Claim 24 wherein the cellulose is present in an amount of between from about 35 to about 45 wt % of the component composition.

26. Use as claimed in any of Claims 23 to 25 wherein the cellulose is present in an amount of about 30 wt % of the component composition.

27. Use as claimed in any of the preceding claims wherein the component composition consists essentially of prednisolone or a pharmacologically acceptable salt or derivative thereof, rheology modifying agent, sugar and cellulose.

28. Use substantially as hereinbefore described with reference to the accompanying examples.

29. A process for the production of particles for use in a pharmaceutical composition, said process comprising the steps of:

mixing water with a component composition comprising at least prednisolone or a pharmacologically acceptable salt or derivative thereof and a rheology modifying agent to produce a paste;

extruding at least a portion of the paste to form extrudate;

spheronising at least a portion of the extrudate to form spheronised particles; and

drying at least a portion of the spheronised particles.

30. A process as claimed in Claim 26 wherein the amount of water used is between from about 180 to about 190 wt % of the weight of the component composition and, where the spheronising step uses a rotation 70 cm plate, the plate does not rotate at about 33 rpm.

31. A process as claimed in Claim 29 or Claim 30 wherein the process comprises any of the features defined in Claims 2 to 28.

32. A process substantially as hereinbefore described with reference to the accompanying examples.

ABSTRACT

Process for Producing Particles for Pharmaceutical Compositions

Water is used to control particle size in a process comprising mixing water with a composition comprising prednisolone or a pharmacologically acceptable salt or derivative thereof and a rheology modifying agent and possibly sugar and cellulose to produce a paste. The paste is extruded to form particles which are then spheronised and dried. One advantage of using water to control particle size is that the number of particles having a diameter within a required range, e.g. between from about 800 to about 1500 μm, may be increased.

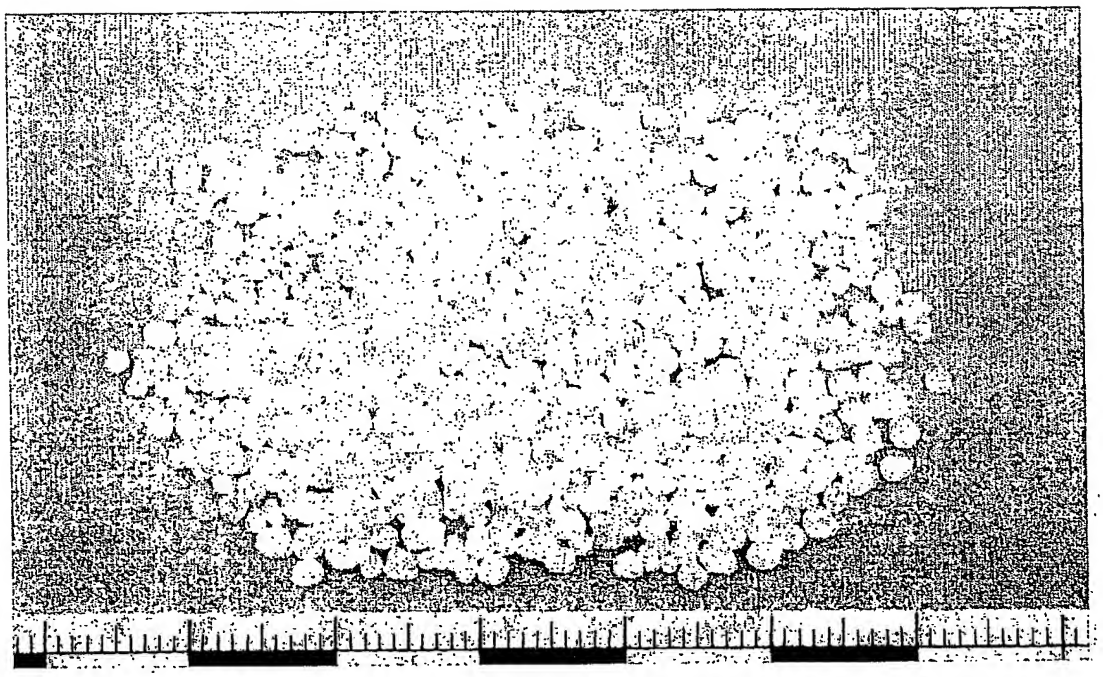

FIGURE 1

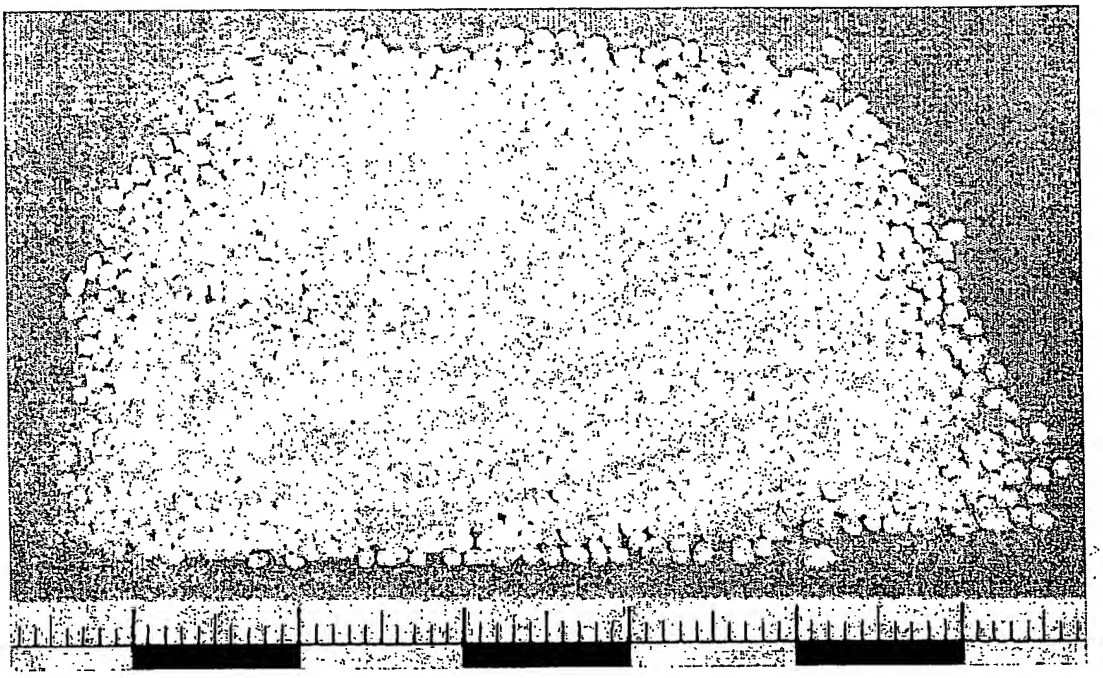

FIGURE 2

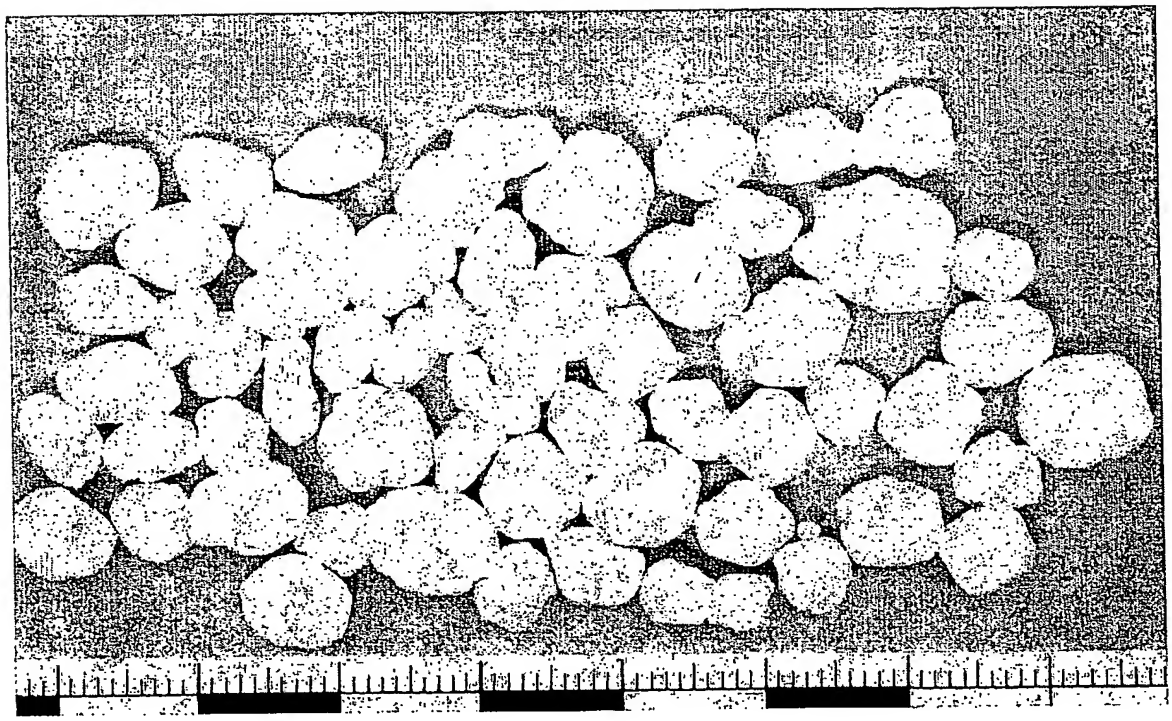

FIGURE 3

Document made available under the Patent Cooperation Treaty (PCT)

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